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Protease-Activated Receptor-2: A Multifaceted Molecular Transducer in the Human Skin

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Dear Editor:

In the last issue of *Annals of Dermatology*, an exploratory study on the role of protease-activated peceptor-2 (PAR-2) in human skin was published by Shin et al.¹. In consideration of the assumed impact of PAR-2 in a variety of normal physiological processes as well as pathophysiological conditions², this is considered a timely and contributive study.

In the study, Shin et al.¹ detected a high expression of PAR-2, particularly in the stratum granulosum of normal human skin, as well as in the acrosyringium of the eccrine sweat glands, while PAR-2 immunoreactivity was weak in the granular layer of the palmar epidermis. This is a highly interesting observation considering the established somatosensory role of the PAR-2. In the skin, the PAR-family and PAR-2 in particular, is richly expressed on cutaneous primary sensory afferent nerve terminals known to convey the sensation of pruritus. These PAR-2-positive fibers are shown to be densely innervating the granular layer of non-glabrous skin. In a number of *in vivo* and human psychophysical studies, PAR-2 and its co-effector transient re-

ceptor potential cation channel A1 (TRPA1) has been associated with the non-histaminergic pruritic pathway wherein superficial polymodal c-fibers transmits the sensation of itch in response to a number of chemical stimuli, including mucunain, tryptase and the agonist applied in Shin et al.'s study¹; SLIGRL-NH₂³. Activity in the non-histaminergic pathways of itch is thought to be a substantial contributor to the chronic itch associated with prevalent conditions such as atopic dermatitis and psoriasis, and the main reason that the itch accompanying with these conditions respond poorly to antihistamines. Steinhoff et al.⁴ (2003) have directly associated PAR-2-signalling with the occurrence of treatment resistant itch in atopic dermatitis and conclude that the receptor is likely to contribute to exacerbate the ongoing inflammatory processes directly by pro-inflammation and indirectly by induction of scratching. Additionally, Shin et al.¹ found that human epidermal keratinocytes (SV-HEKs), which were fully differentiated displayed significantly higher PAR-2 expression than undifferentiated keratinocytes, which is in accordance with similar previous findings. This corresponds well with the

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fact that both aforementioned skin conditions; atopic dermatitis and psoriasis involves substantial epidermal hyperplasia⁵, in addition to PAR-2 associated sensory symptoms, most prominently itch, cutaneous inflammation and mild pain.

It is unclear if PAR-2 is involved in the pathogenesis of inflammatory skin conditions or whether aberrations in PAR-2-signaling is a consequence of preceding etiological processes, which could be distinct between different pathophysiological conditions. However, PAR-2 does appear to play a significant role in skin physiology, inflammation and the related cutaneous sensory symptoms such as itch and pain. This makes the receptor an interesting pharmaceutical target for inflammatory skin diseases.

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Betamethasone Butyrate Propionate Inhibits the Induction of Thymic Stromal Lymphopoietin in Cultured Normal Human Keratinocytes

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Dear Editor:

Thymic stromal lymphopoietin (TSLP), a key epithelial cell and keratinocyte-derived cytokine, has been shown to directly trigger allergic inflammation and the atopic march^{1,2}. Therefore, suppression of TSLP expression should be a rational therapeutic strategy for allergic disorders such as atopic dermatitis (AD). In addition, topical treatments

seem to be suitable for this strategy, since TSLP is produced in epithelia such as the epidermis. Topical glucocorticoid (GC) is the most popular treatment for AD and therefore, it is rational to examine the effects of GC on the expression of TSLP in keratinocytes. In fact, it has been shown that a GC, such as dexamethasone (Dex), but not calcineurin inhibitors, suppresses the expression of TSLP

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